

Vitamin D and UV exposure in chronic kidney disease

Rolfdieter Krause

Nephrological Center Berlin-Moabit; (KfH) Kuratorium for Dialysis and Kidney Transplantation; Research Group Medical Heliotherapy at the Department of Clinical Natural Medicine; Charité University Medical Center; Berlin, Germany

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Abbreviations: UV, Ultraviolet; DE-QCT, Double-Electron Quantitative Computed Tomography; ECG, Electrocardiography; RR, Interval of successive R's; R, Peak of the QRS Complex of ECG; B-B-Diff, SD(dRR), standard deviation of RR intervals; HR, Heart Rate; BP, Blood Pressure; BPs, systolic BP; BPD, diastolic BP; max, maximum Work Load

With loss of renal function and decreasing glomerula filtration rate the serum levels of 25-hydroxyvitamin D [25(OH)D] as well as 1,25-dihydroxyvitamin D [1,25 (OH)₂D] often decrease simultaneously. In representative groups of German patients on renal replacement therapy (hemodialysis, peritoneal dialysis, kidney transplantation) our group retrospectively analyzed the vitamin D status over a period of 12 y (1995–2006). Only 11% of patients had a serum level of 25(OH)D that was > 30 ng/ml, more than 70% had a level of 25(OH)D < 20 ng/ml. In clinical trials we used sun-simulating artificial lamps to produce vitamin D₃ in the skin. Partial-body irradiation (15% of body surface) was used during the routine hemodialysis treatment. Whole-body UV exposure was done in a standing position three times a week before the hemodialysis treatment. With both procedures we observed an increase of the serum level of 25(OH)₂D₃ by approx. 35–50% over a period of 2–3 mo, maintenance of trabecular bone mineral density and a normalization of systolic and diastolic blood pressure. Heart rate variability improved during the whole-body radiation intervention period by 20–25%. Patients who continued the whole-body irradiation regularly two or three times before starting the routine hemodialysis session had maintained normal levels of circulating 25(OH)D₃ and of 1,25(OH)₂D₃. Therefore, from our data it can be recommended that intermittent suberythemal UVB exposure with a sun-simulation spectrum is effective to treat and/or protect against vitamin D deficiency in chronic and end-stage kidney disease patients.

Introduction

Normal kidney function is required for the maintenance of sufficient serum levels of 1,25(OH)₂D. 25-hydroxyvitamin D₃ [25(OH)D₃, caldiol] is the precursor for the activation to

1,25-dihydroxyvitamin D [1,25(OH)₂D₃, calcitriol] in numerous non-renal cells and in the renal proximal tubular cell by the 1-α-hydroxylase. With loss of renal function and decreasing glomerula filtration rate the serum levels of 25(OH)D as well as 1,25(OH)₂D decrease simultaneously because the endocytotic receptor megalin reduces the uptake of 25(OH)D from the vitamin D-binding protein (DBP) and the uptake of 25(OH)D₃ from the glomerular ultrafiltrate.¹ Therefore the KDIGO Clinical Practice Guidelines recommend that for holding a normal status of vitamin D a serum level of 25(OH)D < 20–32 ng/ml should be corrected using the same treatment strategies recommended for the general population.^{2–4} As in the general population and in patients with CKD and ESKD there is an association of low 25(OH)D serum levels with increasing mortality.^{5–7}

Vitamin D Status in German Patients on Renal Replacement Therapy

Renal replacement therapy (RRT) has been established for more than 50 y, and the main focus is to prolong a high quality of life with a low rate of comorbidities. Up to now the majority of patients are older than 65 y, and the major consequences of RRT are essential hypertension, diabetes mellitus type II and metabolic syndrome.^{3,4} For these primary renal diseases vitamin D deficiency is a major risk factor.

In representative groups of patients on renal replacement therapy (hemodialysis, peritoneal dialysis, kidney transplantation) our group retrospectively analyzed the vitamin D status over a period of 12 y (1995–2006).^{8–10} Only 11% of patients had a serum level of 25(OH)D > 30 ng/ml, whereas more than 70% had a level of 25(OH)D < 20 ng/ml. Over the 12 y period an increase of the median of serum level of 25(OH)D from 8.5 ng/ml to 21.0 ng/ml was seen⁹ (Fig. 1). Patients with Diabetes mellitus type I (50%), Diabetes mellitus type II (70%), patients with hypertensive nephropathy (42%) and with immune-systemic diseases (48%) had severe deficiency of 25(OH)D < 12.5 ng/ml.⁸

As reported for the general population the typical seasonal variation of the vitamin D status was observed in patients on renal replacement therapy and also in patients on hemo-dialysis.^{11–19}

Correspondence to: Rolfdieter Krause; Email: rolfdieter.krause@t-online.de
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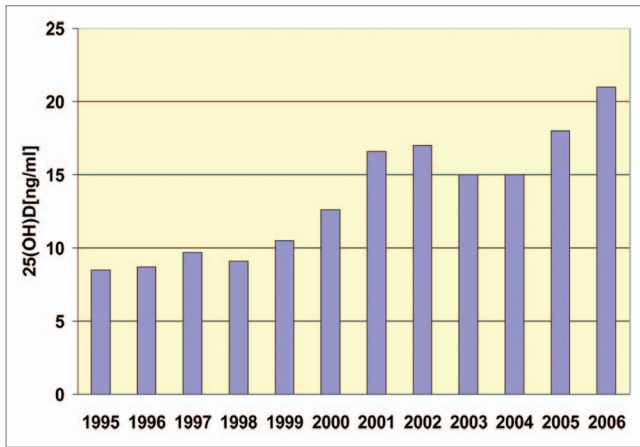


Figure 1. Vitamin D Status of German Hemodialysis Patients (Medians over the time course 1995 – 2006).

The KDIGO group²⁻⁴ reported a correlation between vitamin D status and mortality^{8,10} (Fig. 2). Also for mortality there was a seasonal variation with the highest rates during winter and early springtime and the lowest rates during summer and the early autumn months.²⁰⁻²⁷

Exposure to UV Radiation in End-Stage Kidney Disease (ESKD) Patients

Treatment with vitamin D metabolites and analoges was been used nearly as long as chronic dialysis therapy was established. Due to the main goal of suppressing secondary hyperparathyroidism for improving renal bone disease the medication 1,25(OH)₂D₃, calcitriol was introduced in the early 1970s. Within the past 20 y it has become evident that many organs can synthesize 1,25(OH)₂D₃ by an autocrine mode via local activation of circulating 25(OH)D₃ to 1,25(OH)₂D₃.¹³

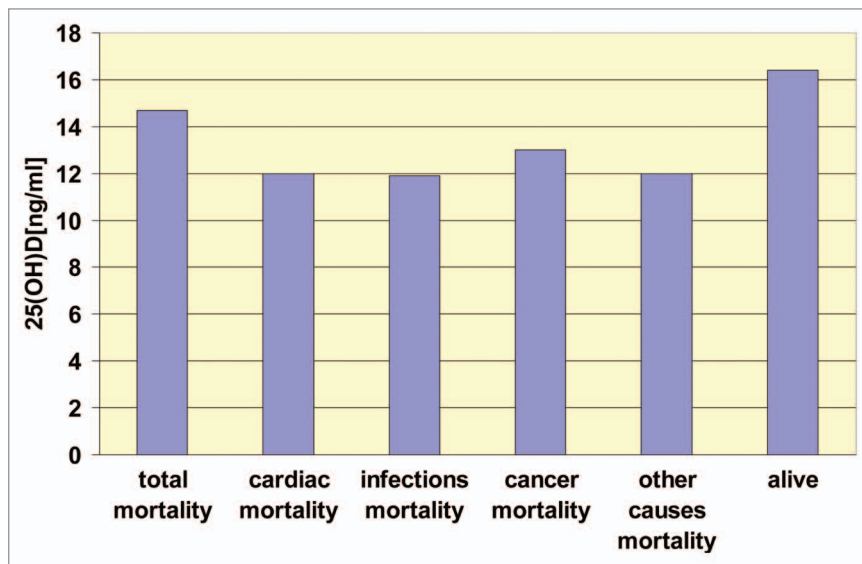


Figure 2. Vitamin D Status and Mortality in German Hemodialysis Patients (Medians over the time course 1995–2006).

The major source of vitamin D comes from exposure of the skin to sunlight and UV-B exposure.^{13,19} The capacity of the skin to produce vitamin D₃ is dependent on skin pigmentation, latitude, season of the year and time of the day.¹⁹ Additionally, aging and alterations of the skin due to uremia with increased pigmentation and hyperkeratosis reduces the capacity of the skin to produce vitamin D₃ when compared with younger and healthy people. It is well known that the skin itself is not only able to convert 7-dehydrocholesterol (7-DHC) to vitamin D₃ (cholecalciferol), but is also able to convert vitamin D₃ to 25(OH)D₃ as well as to the hormonal active metabolite 1,25(OH)₂D₃ by cutaneous 25-hydroxylase [CYP27A, 1/CYP2R1] and 1- α -hydroxylase [CYP27B1], respectively.²⁸⁻³⁶

Therefore the hypothesis of our group was to expose the skin of ESKD patients to UVB radiation to improve serum levels of 25(OH)D and at the same time have the skin also produce 25(OH)D₃ from cutaneous vitamin D which in turn could be converted in the skin to 1,25(OH)₂D₃.³⁷⁻⁴⁴ Moreover, the activation of the whole vitamin D metabolic pathway due to UV irradiation could additionally improve the residual capacity of the endocrine function of the kidneys in CKD patients to produce more of 1,25(OH)₂D₃. Patients with advanced kidney disease stages 3–5 have been reported to need supra-physiological serum levels of > 100–250 ng/ml for converting 25(OH)D₃ extra-renally to 1,25(OH)₂D₃.⁴³

It is also known that in patients who were anephric had detectable serum levels of 1,25(OH)₂D₃.³¹

Medical Heliotherapy in ESKD Patients

For our clinical trials we used sun-simulating artificial lamps with two different procedures.

One procedure was partial-body irradiation during the routine hemodialysis treatment.⁴⁸ We used a tripod-leg-based UV-device (Fig. 3) for irradiating only the ventral part of the legs (e.g., approximately 15% of body surface) with fluorescent lamps (FL) and an UVB output of approx. 3.5%.^{46,48} Whole-body UV exposure (Fig. 4) was done in a standing position three times a week before the hemodialysis treatment. The halogen lamps had an UVB output of ~11%, and there was a gap of 14 percent between E_{VitD} and E_{erythema} for safe sub-erythemal activation of the vitamin D production in the skin; this gap we called the “Therapeutic Window”.⁴⁵⁻⁴⁷ With both procedures we calculated a nonlinear correlation of the vitamin D weighted irradiance dose and the serum level of 25(OH)D₃.⁴⁶

During six months of the whole-body irradiation the medians of all vitamin D metabolites (vitamin D₃, 25(OH)D₃, 1,25(OH)₂D₃) increased, but with different time courses. Vitamin D₃ increased 6-fold after seven weeks from 6 ng/ml to 36 ng/ml, and thereafter a stable plateau was observed over the following

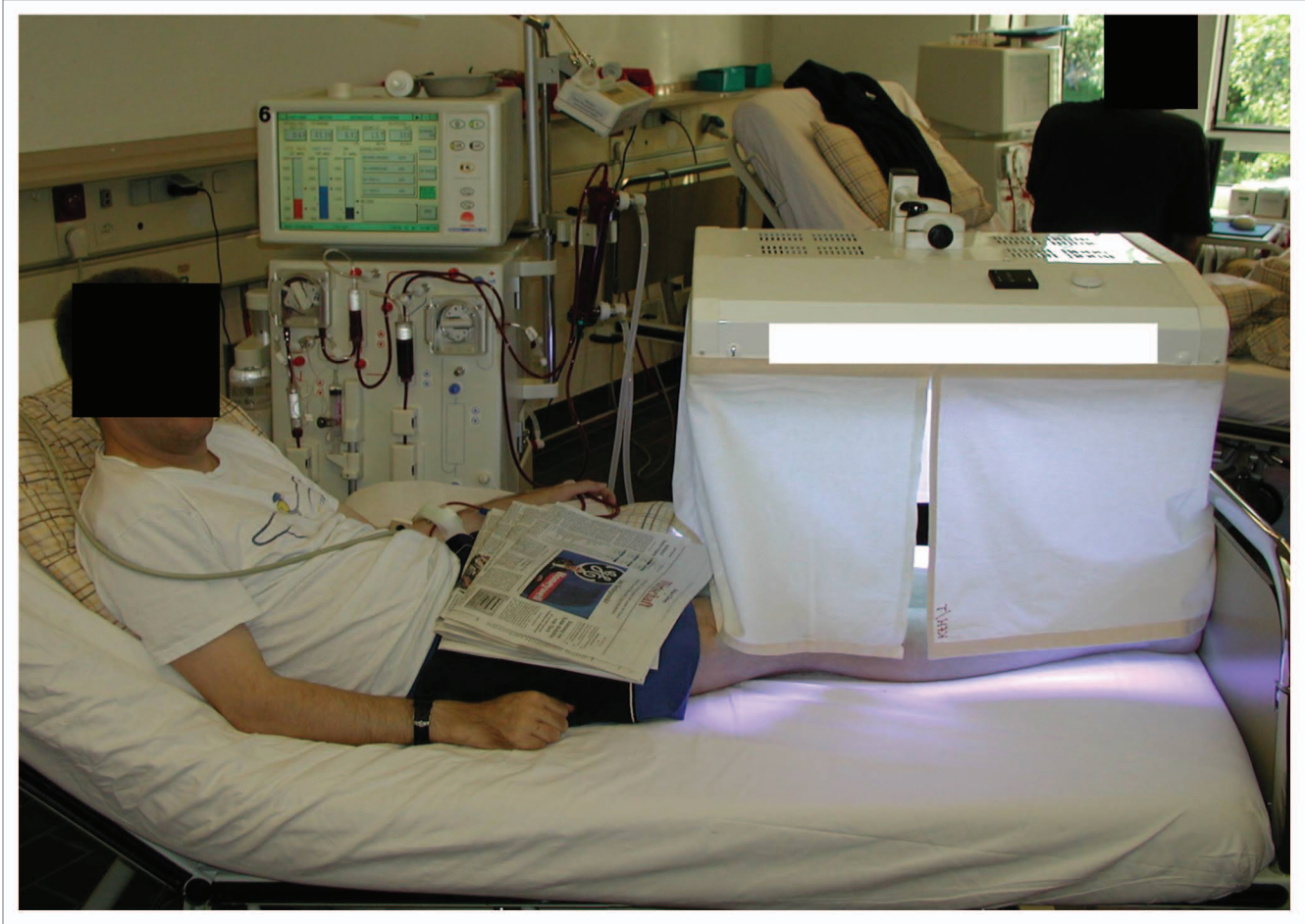


Figure 3. Partial-body UV irradiation during a routine hemodialysis session (from 46, with permission).

months. $25(\text{OH})\text{D}_3$ increased continuously over the six month period by 100% from 43 ng/ml to 86 ng/ml and $1,25(\text{OH})_2\text{D}_3$ increased after seven weeks by 48% from 21 pg/ml to 33 pg/ml remaining stable within the normal range over the following time.⁴⁵ (Fig. 5) After partial-body irradiation we observed an increase of $25(\text{OH})\text{D}$ levels reaching its maximum after ten weeks by ~36% from 25 ng/ml to 39 ng/ml.

The serum level of circulating $1,25(\text{OH})_2\text{D}_3$ increased by 48% after 14 weeks from 10 pg/ml to 19 pg/ml remaining stable thereafter.^{46,48} (Fig. 6).

Whole-body irradiation was able to increase the serum level of $25(\text{OH})\text{D}_3$ by ~50–65% over a period of 3–6 mo.^{45,46} Moreover, as documented in healthy people, regular partial-body UVB exposure of only ~15% of body surface was sufficient to guarantee a high-normal serum levels of $25(\text{OH})\text{D}_3$ and was comparable with whole-body exposure. The exposures mimic the action of the natural sun producing previtamin D_3 in the skin which converts to vitamin D_3 .¹⁹ Once formed it is converted in the liver to $25(\text{OH})\text{D}_3$ which in turn is converted in the kidneys and by activated monocytes and possibly by keratinocytes to $1,25(\text{OH})_2\text{D}_3$.^{31,34,43}

The accumulation of each suberythemal radiation led to a total of 15–35 MED_{II} over the period of 2–3.5 mo, which is equal

to between one-sixth and one-third of the recommended minimal erythemal dose per person over one year.⁴⁶

Skeletal and Cardiocirculatory Effects of UV Exposure in ESKD Patients

Renal bone disease and bone mineral density (BMD). Renal osteodystrophy and extraskeletal calcification are very frequent in CKD and ESKD patients. The established treatment is oral and/or intravenous active vitamin D. But, important side-effects are hypercalcemia and/or hyperphosphatemia. Therefore a vitamin D therapy without these side-effects is needed.

Before and after six months of whole-body exposure to UV radiation there was only a small decrease of 3.5% in the trabecular bone mass in comparison with 11% in the non-irradiated and non-treated control group.⁵⁰⁻⁵² (Fig. 7) This is agreement with the literature reporting a decrease of BMD by ~3% over six months in patients treated with $1,25(\text{OH})_2\text{D}_3$ or analogs.⁵⁴⁻⁶²

Blood pressure regulation. About 50 percent of patients with ESKD suffer from essential hypertension and/or diabetes mellitus type II and metabolic syndrome.^{63,64} Left ventricular hypertrophy, coronary heart disease and cardiomyopathy are very frequent co-morbidities in CKD and ESKD patients. After

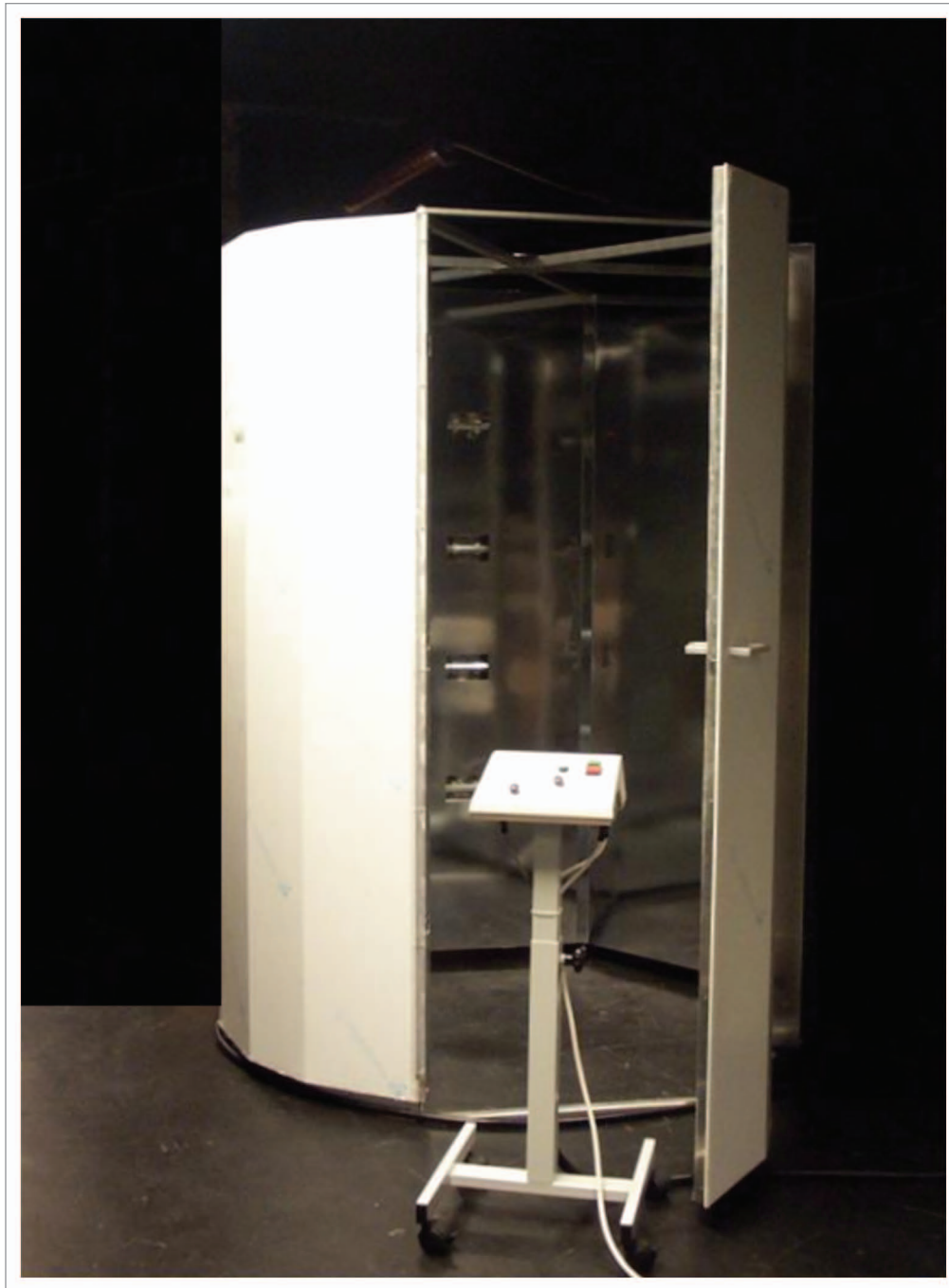


Figure 4. Sun-simulating UV irradiation cabin (from 46, with permission).

seven and 14 weeks of UVB exposure systolic and diastolic blood pressure decreased significantly at rest and also after maximum ergometric work load (Fig. 8). This was comparable with the maximum increases of circulating $25(\text{OH})\text{D}_3$ and $1,25(\text{OH})_2\text{D}_3$. There was a decrease of resting heart rate of 3% and a significant reduction of systolic and diastolic blood pressure of 8% and 4%, respectively.^{47,49} This is also in line with the well-known seasonal and geographic differences of blood pressure with a decrease during summertime and an increase with higher latitude.⁶⁵⁻⁶⁸

Work load capacity. The physical capacity of CKD patients decrease due to, e.g., uremic myopathy, polyneuropathy or metabolic acidosis. Vitamin D deficiency also leads to muscle weakness and to a decrease of muscle strength and coordination. Confirming previous findings from our group and from the literature in healthy people and in cardiac patients submaximal and maximal ergometric work load increased significantly in the group exposed to UV radiation.^{47,49,53} After three months of serial UVB irradiation we found a significant increase of work load by 6% in the bicycle ergometer test, with a significant increase in oxygen uptake of 11%

and a reduction of the accumulation of lactic acid of 9%.⁴⁶

Heart rate variability. In dialysis patients the rate of cardiac death is more than doubled in comparison with the general population, and often they die from sudden death. The uremic neuropathy may be one risk factor for an increase of the sympathetic tone, and heart rate variability (HRV) is one marker of the sympathetic-parasympathetic balance.^{46,69-71}

During the whole-body UV radiation intervention period we found an increase of the medians of the RR-interval time in ECG by 20% and of the means of the standard deviation of the RR-intervals (beat-to-beat difference) by 25%.⁴⁶ (Fig. 9) These are measures of the cardio-circulatory rhythmicity and shows that the neuropathic induced stiffness of the heart frequency distribution decreased. The improvement of these parameters of HRV was observed at the time when the serum level of 1,25(OH)₂D₃ reached its maximum. Therefore serial sun(-like) UV exposure can improve the parasympathetic tone and can protect from arrhythmic dysregulation of the heart. Therefore UV exposure improved the cardio-circulatory adaptation in an equal manner as endurance training.⁶⁹

Use of UVB Radiation in Our Dialysis Unit

Following the clinical trials we had implemented serial UV-B irradiation for the treatment of the renal vitamin D deficiency instead of treatment with vitamin D₃ orally and/or 1,25(OH)₂D₃ intravenously over the past 15 y in our dialysis unit.⁴⁶

A number of patients were exposed intermittently to suberythral whole-body UV-B radiation regularly two or three times before their routine hemodialysis session. These patients hold normal levels of circulating 25(OH)D₃ (mean serum levels: 45.3 ng/ml) and also normal level of circulating 1,25(OH)₂D₃ (mean serum levels: 30.4 pg/ml).

Conclusion

The vitamin D deficiency in CKD patients and especially in patients on dialysis is an independent risk factor for the function

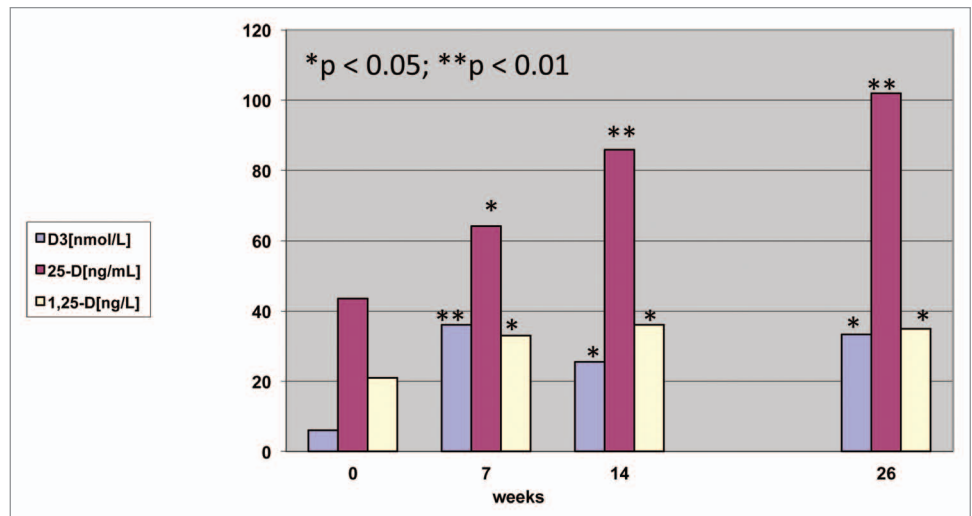


Figure 5. Vitamin D Metabolite Levels in Hemodialysis Patients after Whole-Body UV Irradiation.

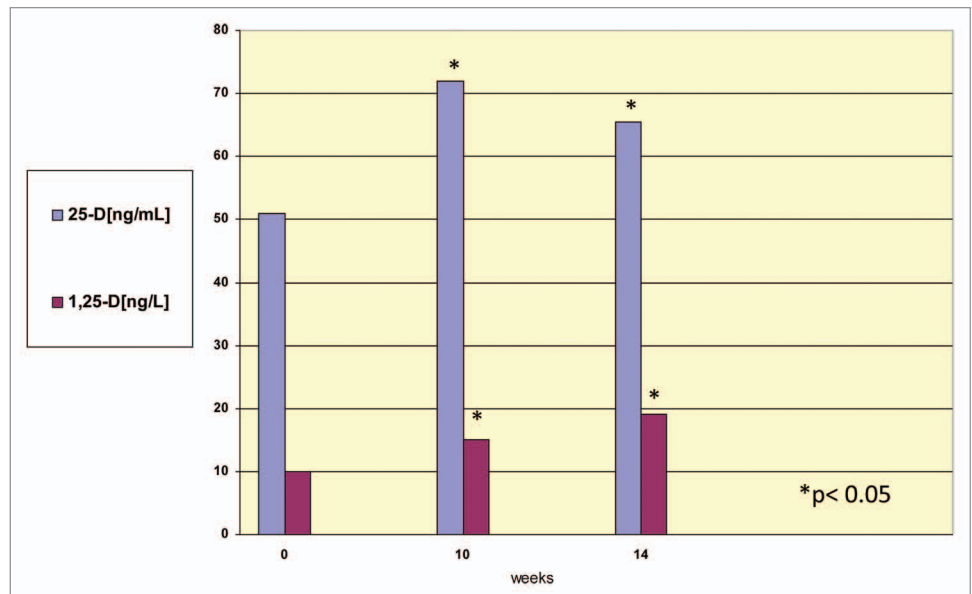


Figure 6. Vitamin D Metabolite Levels in Hemodialysis Patients after Partial-Body Irradiation (approx. 15% of Body Surface).

of many organs and/or metabolic and enzymatic pathways, as well as for the overall and cardiovascular mortality. Additionally impairment of the vitamin D metabolism due to CKD causes a reduction of the physical capacity and multiple co-morbidities. People with renal insufficiency often are also sun deprived.⁷²⁻⁷⁶

As recommended in the K/DOQI guidelines improvement in vitamin D status can result to non-calcemic benefits of vitamin D by the autocrine production of 1,25(OH)₂D₃. The K/DOQI guidelines recommend to normalize the basal vitamin D status. The traditional therapy still used today in nephrology is the use of active vitamin D metabolites to treat secondary hyperparathyroidism. But, using active vitamin D metabolites however can have side-effects causing hypercalcemia, hyperphosphatemia

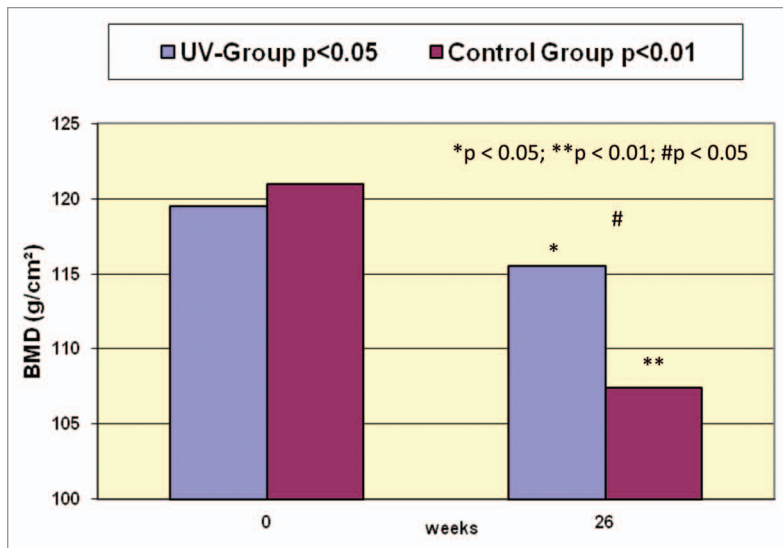


Figure 7. Trabecular Bone Mineral Density (DE-QCT) of Hemodialysis Patients before and after 6 Months of Whole-Body UV Irradiation.

and vascular calcification.^{2,3} Therefore our aim was to use the extrarenal capacity of the monocytes and possibly of the skin to produce 1,25(OH)₂D₃. From our results uremic skin is able to produce a sufficient amount of vitamin D₃ which is metabolized in the liver to 25(OH)D or possibly by the skin and/or other organs and cells to both 25(OH)D and 1,25(OH)₂D₂, then sending it into the circulation and stimulating the well-known positive protective effects in bone, blood pressure regulation, heart rate rhythmicity, as well as on muscle metabolism and physical capacity. From our data it can be recommended that intermittent suberythemal UVB exposure with a sun-simulation spectrum to treat and/or protect the vitamin D deficiency in chronic and end-stage kidney disease patients. We had found no (major) side effects from this therapy over the past 20 y.

Therefore, regular outdoor sun exposure during summertime (April to September/October in latitudes > 45°N/S) and/or serial suberythemal sun-simulating UV-B irradiation should also be recommended as measures of prevention and treatment of patients with all stages of chronic kidney disease.

Disclosure of Potential Conflicts of Interest

No potential conflict of interest was disclosed.

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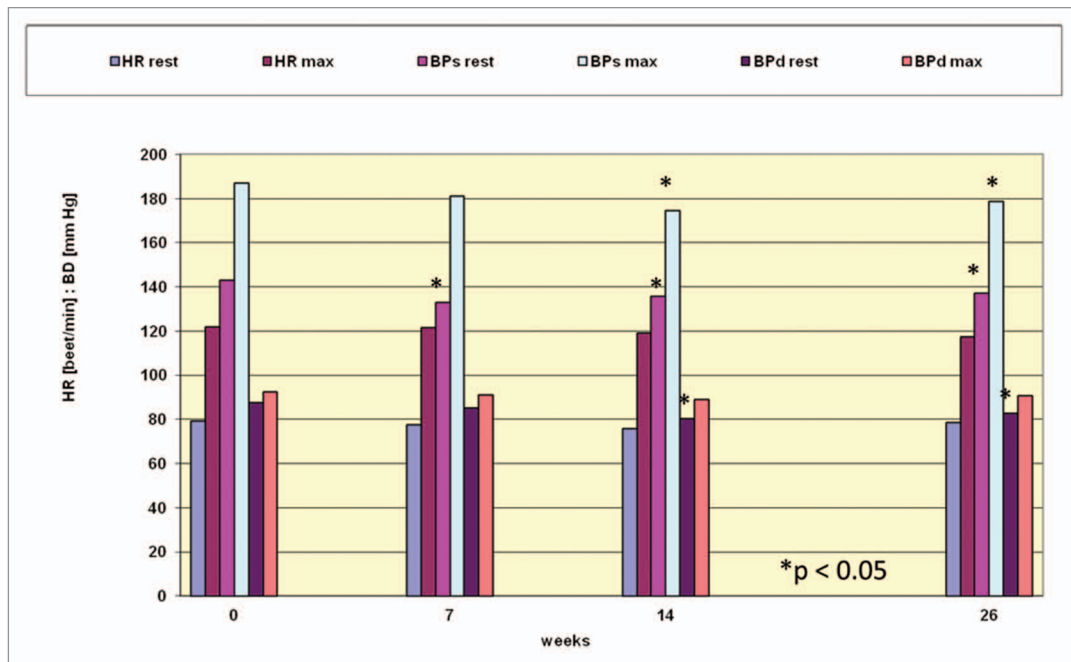


Figure 8. Heart Rate, Systolic and Diastolic Blood Pressure at Rest and at Maximal Work Load of Hemodialysis Patients before and after 6 Months of Whole-Body UV Irradiation.

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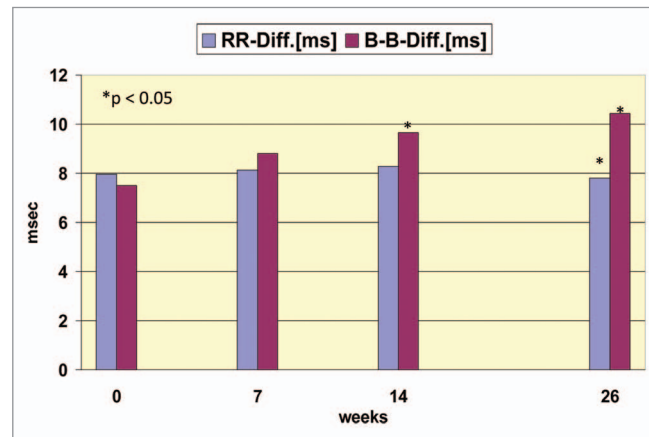


Figure 9. Heart Rate Variability (ECG-RR-Differences and SD(dRR)) of Hemodialysis Patients before and after 6 Months of Whole-Body UV Irradiation.

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